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| EXAMINER | |
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| HIBBERT, CATHERINE S | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/849,498 | YANG ET AL. | |
| | Examiner | Art Unit | |
| | CATHERINE HIBBERT | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-5,8-16,44 and 49-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 8-16, 44 and 49-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 June 2010 has been entered.

Claims 2, 6-7, 17-43 and 45-48 are cancelled. Claims 1 and 44 are currently amended. Claims 1, 3-5, 8-16, 44 and 49-54 are pending and under examination in this action.

### *Response to Amendment*

All rejections not repeated are withdrawn herein.

### *Claim Objections*

Claim 12 is objected to for failing to depend from a preceding claim. See MPEP 608.01(n). It is noted for clarity of the record that claim 12 depends from claim 15. Appropriate correction is required.

### *New grounds of rejection necessitated by amendment*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 12, 13, 14, 15 16, 49-51 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 13, 14, 16, 49, 50, and 54 each recite the limitation "backbone" in line 1. There is insufficient antecedent basis for this limitation in these claims. The independent claims 1 and 44 are currently amended to now recite the term "polyester backbone" and since the base claims also refer to polymers which inherently have "backbones" it is indefinite whether the references to "backbone" are necessarily to the newly amended term "polyester backbone".

Claims 12, 15, and 51 are indefinite insofar as they depend from claims 11 and 50.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims **1, 3-5, 8-16, 44 and 49-54** are rejected under 35 U.S.C. 103(a) as being unpatentable over Liggins & Burt in "Polyether-polyester diblock copolymers for the preparation of paclitaxel loaded polymeric micelle formulations" (Advanced Drug Delivery Reviews, 2002, Vol. 54, pages 191-202) in view of Mahato et al (US Patent 6,696,038, filed 14 September 2000, entire document) and further in view of Lollo et al (USPGPub 2003/0134420A1, entire document, filed 2 August 2002, published 17 July 2003, of record).

Currently amended claim 1 is drawn to an article for delivering a drug and a nucleic acid, the article comprising:

> a nanoparticle forming a micelle, wherein the nanoparticle comprises a polymer having a polyester backbone;
>
> a nucleic acid (i.e., DNA; claim 4) associated with an exterior of the micelle; and
> a drug associated with an interior of the micelle (claim 1).

Claim 3 is drawn to the article of claim 1 and specifies that the nanoparticle is capable of passing through a cell membrane.

Claim 5 is drawn to the article of claim 1 and specifies that the drug is a cancer drug.

Claim 8 is drawn to the article of claim 1 and specifies that the nanoparticle is stable at a concentration of greater than 5 mg/L.

Claim 9 is drawn to the article of claim 1 and specifies that the nanoparticle is capable of crossing the blood/brain barrier.

Claim 10 is drawn to a composition comprising the article of claim 1 and a pharmaceutically acceptable carrier.

Claim 11 is drawn to the article of claim 1 wherein the backbone comprises tertiary amines. Claim 15 is drawn to the article of claim 11 wherein at least a portion of the tertiary

amines are quaternized and bound to a hydrophobic side chain. Claim 12 depends from claim 15 and is drawn to the article of claim 15 wherein the hydrophobic side chain comprises cholesterol. Claim 13 is to the article of claim 11 wherein the backbone comprises a copolymer of quaternized and non-quaternized tertiary ammonium groups.

Claim 14 is drawn to the article of claim 1 wherein the backbone further comprises an ether linkage. Claim 16 is to the article of claim 1 wherein the backbone further comprises a polyether.

Claim 50 is to the article of claim 1, wherein the backbone comprises an amphiphilic co-polymer. Claim 51 is to the article of claim 50, wherein the amphiphilic co-polymer is a cationic amphiphilic co-polymer.

Claim 54 is drawn to the article of claim 1, wherein the backbone comprises a graft co-polymer.

Claim 52 is drawn to the article of Claim 1 wherein the drug is not covalently or ionically bound to the nanoparticle. Claim 53 is drawn to the article of Claim 1 wherein the drug is physically contained by the nanoparticle.

Currently amended claim 44 is drawn to a kit/composition comprising:

a container including an amphoteric polymeric nanoparticle forming a micelle, wherein the polymeric nanoparticle comprises a polymer having a polyester backbone;

a nucleic acid associated with an exterior of the micelle;

a drug associated with an interior of the micelle; and

instructions for administering the nanoparticle to a subject.

Claim 49 is to the kit/composition of claim 44, wherein the backbone comprises a graft co-polymer.

Liggins & Burt teach articles/compositions for delivery of the cancer drug paclitaxel comprising amphoteric polymeric nanoparticles forming a micelle, wherein the polymeric nanoparticle comprises a polymer having a polyester backbone; a nucleic acid (i.e., DNA; claim 4) associated with an exterior of the micelle; a drug associated with an interior of the micelle; and instructions for administering the nanoparticle to a subject. For example, Liggins & Burt recite the "development of formulations for paclitaxel employing polyether-polyester diblock copolymers as micelle forming carriers" (abstract). Regarding the limitations that the drug be associated with an interior of the micelles and especially regarding claims 52 and 53, Liggins & Burt continue that dissolution of "paclitaxel/copolymer matrices in aqueous media resulted in complete solubilization of paclitaxel within the hydrophobic PDLLA core of the micelles" (abstract). In addition, especially regarding claims 14, 16, 50, and 51, the copolymers of Liggins & Burt read on graft copolymers, wherein the backbone further comprises an ether linkage and specifically a polyether and wherein the amphiphilic co-polymer is a cationic amphiphilic co-polymer, stating that diblock "copolymers of methoxypolyethylene glyco-block-poly(D,L-lactide)(MePEG:PDLLA) were synthesized from monomers of D,L-lactide and MePEG by a ring opening bulk polymerization in the presence of stannous octoate" (abstract).

Especially regarding claim 10, Liggins & Burt teach the use of pharmaceutically acceptable carriers (e.g. page 199, under heading: "Biodistribution and pharmacokinetics").

Especially regarding claims 3 and 9, Liggins & Burt teach nanoparticles which are stable at a concentration of greater than 5 mg/L (e.g. see page 199, under heading: "Biodistribution and

pharmacokinetics", showing 25 mg/kg or 100 mg/kg administration of micellar paclitaxel formulated in MePEG:PDLLA 60:40 diblock copolymer, MePEG=2000) and are inherently capable of passing through a cell membrane and crossing the blood/brain barrier (e.g. see page 199, left column paragraph 2, discussing the use of the micelles for delivery of drugs for treatment of diseases of the central nervous system).

It is noted that the terms such as "associated" must be given a very broad interpretation regarding the claim language in part because Applicant provides a broad description in the specification for how molecules may be associated and dissociated with one another for the claimed invention. Applicant recites: "A first molecule may be "associated" with a second molecule, under set conditions, if the two molecules move together as a unit under these conditions. For example, the two molecules may be immobilized with respect to each other. The two molecules may be covalently or ionically bonded, may be joined by Van der Waal's forces or magnetic forces or one molecule may be physically contained or trapped by the second molecule or a collection of second molecules" [instant specification ¶ 0048]. Applicant further recites: "A first molecule may be "disassociated" from a second molecule or article with which it is associated. Disassociated means that the first molecule can move independently of the second molecule. The first molecule can also be disassociated from a second molecule or from an article if the second molecule or article degrades or is broken down so that it is no longer linked to the first molecule" [instant specification ¶ 0049].

Although Liggins & Burt teach an article/composition for drug delivery comprising amphoteric polymeric nanoparticles forming a micelle with a cancer drug associated on the interior of the micelle, they fail to teach the article/composition also comprises a nucleic acid

(i.e., DNA) associated with an exterior of the micelle. In addition, regarding claims 11, 15, 12 and 13, Liggins & Burt fail to teach wherein the backbone comprises tertiary amines, wherein at least a portion of the tertiary amines are quaternized and bound to a hydrophobic side chain, wherein the hydrophobic side chain comprises cholesterol or wherein the backbone comprises a copolymer of quaternized and non-quaternized tertiary ammonium groups.

**Mahato et al** teach articles/compositions for cancer drug delivery comprising cationic lipid polymers (i.e., capable of forming a micelle), nucleic acids (including DNA) which would be inherently associated with an exterior of the micelle (e.g. abstract), wherein the hydrophobic portion of the polymer backbone comprises branched polyethylenimine (PEI) comprising tertiary amines of PEI linked to cholesterol lipid anchors (e.g. Figure 1 and legend; column 2, lines 46-65).

Mahato et al fail to explicitly teach wherein the backbone comprises a copolymer of quaternized and non-quaternized tertiary ammonium groups.

**Lollo et al** teach polymers comprising copolymers of quaternized and non-quaternized tertiary ammonium groups. Lollo et al teach an article for drug delivery wherein a polymer comprises a graft co-polymer having a backbone including tertiary amines, at least a portion of the tertiary amines quaternized and bound to a hydrophobic side chain (claim 11), and further teaches wherein the hydrophobic side chain comprises cholesterol (claims 12 and 54). For example, Lollo et al teaches FIG. 11 shows the structure of grafted polymers with two hydrophobic domains per PEG chain. FIG. 11a shows a hydrophobic domain between the cationic domain and the surface domain. FIG. 11b shows a hydrophobic domain positioned at the

terminus of a surface (e.g., hydrophilic) domain, and between the surface (e.g., hydrophilic) and cationic domains (¶ 0023, lines 1-3) (claims 50-53).

In addition, Lollo et al teach wherein the article forms a micelle and further teach wherein a drug is associated with an interior of the micelle and a nucleic acid is associated with an exterior of the micelle (claims 1 and 44). For example, Lollo et al recite "the invention provides novel molecular complexes, referred to as "polyplexes" containing an anionic compound, such as a nucleic acid, associated with one or, more typically, multiple co-polymer domains, including a cationic domain, a transitional domain, and/or a surface domain (¶ 0005, lines 1-2).

> As shown in FIG. 1, polyplexes of the present invention are made up of multiple co-polymer domains. These domains are organized by the type of functional groups present on the co-polymer making up the domain. Typically, the center domain (Zone I of FIG. 1) contains the anionic agent. Examples of anionic agents include nucleic acids, negatively charged drugs and other small molecules capable of being delivered via a polyplex through a cellular boundary or lipid membrane. The cationic domain (Zone II of FIG. 1) is designed to interact, e.g., electrostatically, with the anionic domain/agent. Generally, the cationic domain is comprised of one or more cationic backbone moieties of copolymers, which are described in greater detail below. The transitional domain (Zone III of FIG. 1) links the cationic domain with the surface domain, typically via linear or branched co-polymers. The transitional domain may be hydrophobic in nature and may be comprised, at least in part, of hydrophobic moieties of copolymers. When the transitional domain is comprised at least in part of hydrophobic moieties, it is generally referred to as the "hydrophobic domain." Finally, the surface domain (Zone IV of FIG. 1) defines the polyplex surface by way of, for example, branching elements which allow the introduction of multiple molecules or other polymers on the polyplex surface. Such moieties modify the surface properties of the polyplex so as to enhance overall delivery of the anionic agent. The surface domain may be comprised, at least in part, of

hydrophilic moieties of copolymers, as well as other ligands and other surface moieties which allow the polyplex to perform its intended function [0032].

In addition, applicants claim the article in claim 1 wherein the drug is a cancer drug and wherein the article is in a composition with a pharmaceutically acceptable carrier (claims 5 and 10). Applicants also claim a kit comprising: a container including an amphoteric polymeric nanoparticle forming a micelle, wherein the polymeric nanoparticle comprises a polymer having a backbone comprising a polyester; a nucleic acid associated with an exterior of the micelle, a drug associated with an interior of the micelle; and instructions for administering the nanoparticle to a subject (claim 44).

Lollo et al teach a micelle complex comprised of amphoteric nanoparticles having a hydrophilic portion associating with DNA and/or cancer drugs and a hydrophobic portion capable of associating with cancer drugs and capable of passing through a cell membrane and capable of being directed to specific membranes by receptor-mediated targeting. In addition, Lollo et al contemplate a multidomain complex which can accommodate nucleic acids either on the interior or exterior and can accommodate drugs either on the interior or exterior (claims 50-52). For example, Lollo et al recite: "Typically, the center domain (Zone I of FIG. 1) contains the anionic agent. Examples of anionic agents include nucleic acids, negatively charged drugs and other small molecules capable of being delivered via a polyplex through a cellular boundary or lipid membrane" (¶ 0032, lines 2-4 and especially ¶ 0031-0038).

Furthermore, Lollo et al anticipate using their invention to treat a subject and although they do not explicitly recite "instructions", it would be inherent that any treatment plan for treating a human subject would inherently require instructions. For example, Lollo et al recite

"A method for treating a subject comprising administering to said subject an effective amount of a penetration enhancer and a polyplex comprising a nucleic acid, a cationic backbone moiety, a hydrophobic moiety, and a hydrophilic moiety, such that said subject is treated" (e.g. see Lollo et al claims 58, 59 and 68). Lollo et al anticipate using the complex to deliver genes and drugs *in vivo* and thus anticipate claims 10 and 44.

Furthermore Lollo et al teach wherein the article forms a micelle and further teaches wherein a drug is associated with an interior of the micelle and a nucleic acid is associated with an exterior of the micelle (claims 1 and 44). For example, Lollo et al teaches partially hydrophobic conjugates also may be used since they possess moieties that preserve sufficient water solubility (since purely hydrophobic molecules are water insoluble). These conjugates can be made up of two different types of grafts, hydrophilic moieties to maintain adequate water solubility (`A`), and hydrophobic moieties (`B`) to introduce a domain with binding and micelle formation properties. In one embodiment, the polymer is designed by grafting two or more of these elements onto a cationic backbone moiety (e.g., a cationic polymer, `C`) (claims 50-51). A suitable grafting element, or hydrophilic moiety for this approach is PEG, which promotes solubility and steric shielding. Another suitable grafting element is any hydrophobic moiety, as described above, which may form domains with binding capabilities. These two or more types of grafting elements can then be randomly distributed along a cationic backbone moiety during the grafting step (¶ 0067, lines 1-6).

In addition, Lollo et al teaches an article as in claim 1 wherein the nanoparticle is stable at a concentration of greater than 5 mg/L because Lollo et al recites "polyplex concentration are reported by DNA content and were 10 ug/ml" which reads on the instant claim 8.

It would have been obvious to one of ordinary skill in the art to have used nucleic acids including DNA associated with the micelles exterior and to have used cholesterol anchors as shown in Mahato et al with quarternized and non-quarternized tertiary amines of Lollo et al in the co-polymer comprising polyethers and polyester backbones on Liggins & Burt because Mahato et al and Lollo et al show they were successfully used in drug delivery micelles.

One of ordinary skill in the art would have been motivated to use nucleic acids for gene therapy purposes as shown throughout Mahato et al and to have used the cholesterol anchors because Liggins & Burt state that the hydrophobic portions of their nanoparticles can be modified for improved micelle formation (e.g., page 194, 3rd paragraph of right column).

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of polyester backbones for the purpose of micellar cancer drug delivery, the association of nucleic acids including RNA and DNA with micellar drug delivery articles/compositions, hydrophobic cholesterol anchors, polyester copolymers and polymer backbones comprising quarternized and non-quarternized tertiary amines were successfully practiced at the time of applicants' invention.

In view of the foregoing, the method of claims **1, 3-5, 8-16, 44 and 49-54** as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)*.

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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